CHAPTER 29

Liver Transplantation

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DEFINITIONS AND EPIDEMIOLOGY

Types of Liver Transplants

Liver transplantation refers to the surgical replacement of a diseased liver with a donor-grafted organ. This is most commonly *orthotopic* (complete removal and replacement), but occasionally *heterotopic*, where the native organ is left in situ. The transplant may be whole liver, a reduced-size liver, or a liver segment, the latter as means of overcoming donor organ scarcity, particularly for pediatric recipients (Figure 29–1). *Reduced-size liver grafts*, such as a left-lateral segment or hemireduction graft, can be derived from either cadaver or living donors, or from *split-liver transplantation*, where two grafts are created from a single donor organ for two recipients, usually an adult and an infant.[1]

MELD and PELD

The United Network for Organ Sharing in the United States has devised the Model for End-stage Liver Disease (*MELD*) and Pediatric End-stage Liver Disease (*PELD*), which are numerical scales that are currently used for liver allocation.[2] Similar systems exist in other countries. These scores are based on a patient's risk of dying while waiting for a liver transplant, derived from objective and verifiable medical outcomes data. The MELD

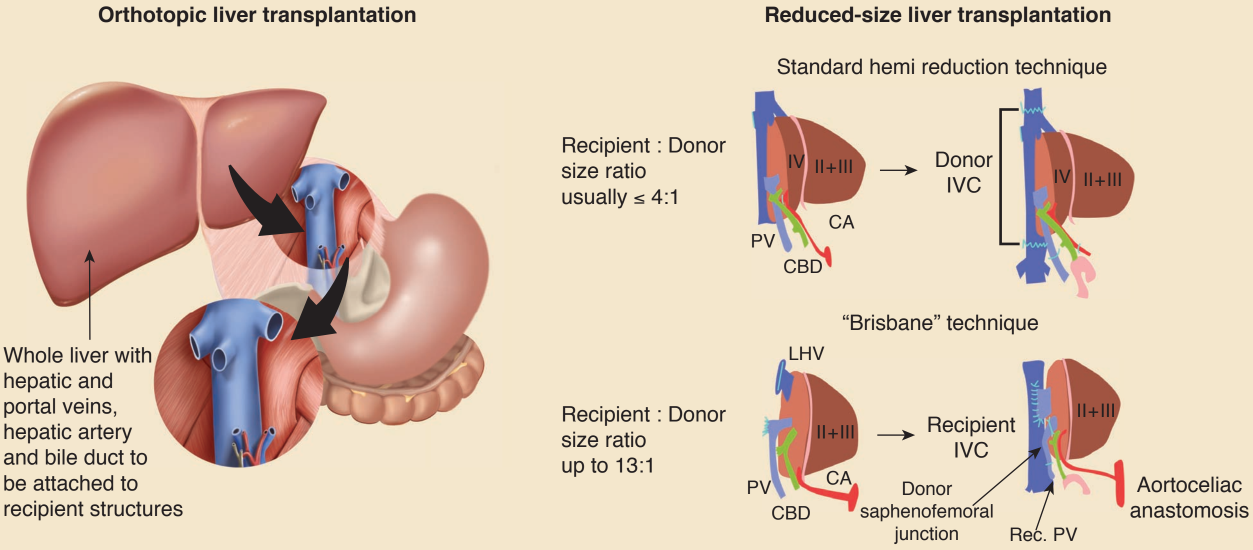
Orthotopic liver transplantation
Whole liver with hepatic and portal veins, hepatic artery and bile duct to be attached to recipient structures
Reduced-size liver transplantation
Standard hemi reduction technique
Recipient : Donor size ratio usually ≤ 4:1
IV
II+III
PV
CA
CBD
Donor IVC
IV
II+III
"Brisbane" technique
LHV
Recipient : Donor size ratio up to 13:1
II+III
PV
CA
CBD
Recipient IVC
Donor saphenofemoral junction
II+III
Rec. PV
Aortoceliac anastomosis

FIGURE 29–1 ■ Surgical techniques for liver transplantation in children. Orthotopic whole-organ replacement, and reduced-size techniques. Donors are matched for size and blood type.

score, used for patients aged 12 years and older, is based on bilirubin, international normalized ratio (INR), and creatinine. The PELD score is based on bilirubin, INR, albumin, growth failure, and age, factors which better predict mortality in children. These scores do not alone determine the likelihood of getting a transplant. Other factors include matched (blood group and size) organ availability, the occurrence of higher priority exceptions (e.g., those with fulminant hepatic failure), and the distribution of MELD/PELD scores for other patients in a local area or region, and consideration for living donation. The PELD/MELD system also has designated exception scores assigned to specific liver conditions that have preserved liver synthetic function and thus corresponding low allocation scores, such as those children with metabolic liver diseases (e.g., urea cycle disorders) and hepatoblastoma. In addition, a program can request a higher exception score if the calculated score does not truly represent the patient's condition. This is done by submitting an exception score request to their UNOS regional review board for consideration.

Epidemiology

The annualized incidence of liver transplantation in the United States is 10–12 per million total population, that is, 50–60 cases per million children/year (1/16,000 children), or about 600 children, one-third of these being infants. Approximately 55% of these transplants are for end-stage chronic liver disease, the majority of these due to biliary atresia (BA); about 25% are for metabolic liver diseases, 10% for acute liver failure, and 5% for liver tumors (Figure 29–2).[3,4] *BA* (Chapter 23) occurs in about 1/14,000 live births in the United States, but not all cases of BA require transplant (see below). Pediatric acute liver failure (PALF) has estimated annualized incidence of about 2 per million, and about 50% recover without transplant.[5] It is notable that the number of long-term survivors of liver transplantation is currently about 10 times these annualized figures. Thus, children who require liver transplantation or are being followed after liver transplantation are likely to be encountered with some frequency in pediatric practice, and the number of these children is expanding.

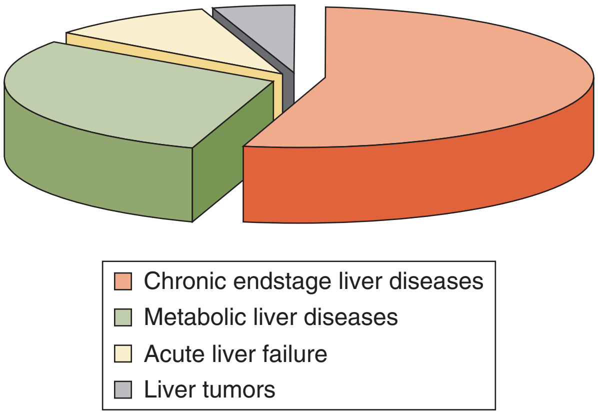

FIGURE 29–2 ■ Relative frequency of types of liver disease for which liver transplantation is indicated in children. Of all pediatric liver diseases, biliary atresia is the most common indication (50%).

CLINICAL PRESENTATION AND REASONS FOR REFERRAL

A wide range of chronic liver diseases in children, a number of liver-specific metabolic diseases, some rare tumors of the liver, and presentations of acute liver failure are potentially cured by liver transplantation. These conditions, although individually rare, are collectively not uncommon, and are accompanied by medical and social demands of lifelong aftercare.

Indications

End-stage chronic liver diseases, such as BA, form the commonest indication, accounting for more than half of all pediatric liver transplant recipients, and the majority of infant recipients (Table 29–1). BA has an incidence of 5–7/100,000 live births in the United States and Europe, and 10–15/100,000 in Asia, and in about two-third of cases, the initial attempt at a bile drainage procedure (hepatoportoenterostomy) fails, and the infant/child develops chronic liver failure.[6] Considered together, *liver-specific metabolic diseases* represent approximately 25% of pediatric liver transplants and are the second most common indications for liver transplant after BA. These can be divided into: (1) those that lead to liver injury, with or without other organ involvement, such as alpha-1-antitrypsin deficiency, Wilson's disease, tyrosinemia, familial cholestasis, and cystic fibrosis (CF); and (2) diseases due to a metabolic defect expressed solely or predominantly in the liver but leading to injury to other organ systems, such as the urea cycle disorders, Crigler–Najjar syndrome, and hyperoxaluria. *Acute liver failure* accounts for about 10% of cases. Most cases are of indeterminate cause, followed by acetaminophen toxicity, other drug toxicities, Wilson's disease, autoimmune hepatitis, and perinatal hemochromatosis. Finally, *unresectable liver tumors* such as hepatoblastoma, embryonal sarcomas, and hemangioendotheliomas are rare but important indications for timely liver transplantation.

Contraindications

Some conditions associated with serious liver involvement are not curable by liver transplantation, namely those with life-threatening extrahepatic disease are absolute contraindications to liver transplantation

Table 29–1.

Indications for Liver Transplantation in Children

	Frequency (% of Transplants)
Chronic end-stage liver diseases (60%)	
■ Biliary atresia	55
■ Chronic active hepatitis	4
■ Primary sclerosing cholangitis	1
Liver-specific genetic/metabolic diseases (25%)	
■ Causing chronic liver injury ± other organ involvement	10
■ alpha-1-antitrypsin deficiency	
■ Familial cholestasis	5
■ Cystic fibrosis	2
■ Tyrosinemia	1
■ Glycogen storage diseases	1
■ Alagille syndrome	5
■ Metabolic defect expressed solely or predominantly in the liver but leading to other organ injury/morbidity	
■ Urea cycle disorders	2
■ Hyperoxaluria	1
■ Crigler–Najjar syndrome	<1
■ Maple syrup urine disease	1
■ Ornithine transcarbamylase deficiency	<1
Acute liver failure (10%)	
■ Indeterminate cause	5
■ Acetomenophin toxicity	2
■ Other drug toxicities	<1
■ Wilson's disease	1
■ Perinatal hemochromatosis	1
■ Some fatty acid oxidation defects	<1
■ Viral hepatitis (hepatitis A, B, C, EBV, adeno, CMV, echo, herpes, parvo)	1
■ Autoimmune hepatitis	
Primary unresectable liver tumors (5%)	
■ Hepatoblastoma	2
■ Embryonal sarcoma	<1
■ Hemangioendothelioma	<1

(Table 29–2). Although in the past there have been some technical and management restrictions with regard to age, size, and the occurrence of hepatopulmonary syndrome and portal vein thrombosis, successful liver transplantation is now possible even in the neonatal period, and the various technical issues have been overcome, and these are considered only relative contraindications. There are some conditions in which the transplant should be temporarily deferred, such as acute active infections and recent live virus immunizations.

Reasons for Referral

Those who might benefit from liver transplantation present with a range of clinical problems, some not necessarily with initial obvious links to the liver (Table 29–3). Early referral for evaluation is emphasized in all cases in which transplantation is even remotely an option to allow for timely assessment, full and frank discussion of options, psychological preparation, appropriate pre-transplant aggressive management, and evaluation of donor options.

Presentation

BA is a special case, in which a "failed Kasai procedure" in infancy, manifesting as a failure to clear jaundice within 3–6 weeks, virtually always portends complications of cirrhosis within weeks to a few months. Thus, as soon as a failed Kasai is realized, referral for transplant

Table 29–2.

Contraindications to Liver Transplantation in Children

Absolute

- Curative alternative therapy available
- Uncontrolled systemic sepsis
- Irreversible neurological injury
- Extrahepatic malignancy
- Progressive terminal non-hepatic disease
- Mitochondrial disorders with progressive neurological involvement

Relative

- Severe hepatopulmonary syndrome—actionable management
- Portal vein thrombosis—vein graft availability
- Active primary peritonitis—temporary deferment
- Active viral infection—temporary deferment
- Recent liver virus immunizations—temporary deferment

evaluation should be made. Similarly, recurrent cholangitis, which can be life-threatening and can result in development of acute or chronic synthetic failure, should be a consideration for transplantation. Beyond that, any presentation with features of end-stage liver disease, such as ascites, portal hypertension, and nutritional growth failure, is a clear indication for referral.

Causes and complications of chronic end-stage liver disease

Any child with chronic liver disease and/or cirrhosis requires regular follow-up, evaluating for signs of end-stage disease, as listed in Table 29–3, the occurrence of which should provoke referral. The complications of chronic liver disease and cirrhosis (listed in Table 29–3) are due to *impaired hepatic function and cholestasis*, which cause nutritional disturbances, jaundice, pruritus, and coagulopathy, and *portal hypertension*, which causes varices, hypersplenism, and hepatorenal or hepatopulmonary syndrome. Encephalopathy and ascites occur as a result of both of these major pathophysiologic events. In addition, impaired immunity with resulting bacterial infection may complicate cirrhosis. Hepatocellular carcinoma can complicate cirrhosis in childhood, particularly in chronic hepatitis B and tyrosinemia type I.

The presentation of some complications can be subtle, such as nutritional growth failure. In some

Table 29–3.

Reasons for Referral for Liver Transplant Evaluation

Chronic end-stage liver diseases

Specific to biliary atresia

- Failed hepatoporoenterostomy (persisting jaundice)
- Recurrent ascending cholangitis
- Any cirrhosis complications listed below

Complications of end-stage liver disease and cirrhosis of any cause

- Nutritional disturbances, growth failure, malabsorption
- Portal hypertension and variceal hemorrhage
- Hypersplenism
- Ascites
- Liver synthetic dysfunction (coagulopathy, hypoalbuminemia)
- Hepatorenal and hepatopulmonary syndromes
- Encephalopathy
- Bacterial infections, spontaneous bacterial peritonitis
- Hepatocellular carcinoma

Liver-specific genetic/metabolic diseases

- Those causing complications of end-stage liver disease listed above ± related morbidities, such as alpha-1-antitrypsin deficiency, familial cholestasis, cystic fibrosis, tyrosinemia, glycogen storage diseases, Alagille syndrome
- Metabolic defects expressed in the liver but leading to other organ injury and/or serious morbidity, and compromised quality of life, such as urea cycle disorders (life-threatening recurrent hyperammonemia and hyperoxaluria (renal failure)), Crigler–Najjar syndrome (brain injury), maple syrup urine disease (brain), ornithine transcarbamylase deficiency

Acute liver failure, presenting as any combination of sudden onset of jaundice, encephalopathy coagulopathy, hypoglycemia, markedly elevated liver transaminases

Primary liver tumors where there is any doubt as to resectability, prior to chemotherapy

Table 29–4.

Stages of Hepatic Encephalopathy in Children

Stage	Clinical	Reflexes	Neurological	EEG
Infant				
Early (I and II)	Inconsolable crying, sleep reversal	Unreliable normal or hyperreflexia	Untestable	
Mid (III)	Somnolence, stupor, combativeness	Unreliable, may be hyperreflexia	Most likely untestable	
Late (IV)	Comatose, arouses with painful stimuli (IVa) or no response (IVb)	Absent	Decerebrate or decorticate	
Older child				
0	Normal	Normal	Psychtesting only	Normal
1	Confused, poor sleep habits, forgetful	Normal	Tremor, apraxia, impaired handwriting	Normal or diffuse slowing
2	Drowsy, decreased inhibitions	Hyperreflexia	Dysarthria, ataxia	Generalized slowing
3	Stuporous, obeys simple commands	Hyperreflexia, up-going toes (+Babinski)	Rigidity	Generalized slowing
4	Comatose, arouses with painful stimuli (IVa) or no response (IVb)	Absent	Decerebrate or decorticate	Abnormal, very slow delta activity

patients, portal hypertension can progress slowly, manifesting only as splenomegaly and hypersplenism (bruising tendency, recurrent epistaxis, and thrombocytopenia). Encephalopathy in children can be very subtle in chronic disease, presenting only as deterioration of school performance, sleep inversion, or intermittent somnolence. In other cases, complications can be dramatic, such as massive ascites and GI bleeding from esophageal varices, and can be the initial presentation of the underlying chronic liver disease.

Metabolic liver diseases causing liver injury are diagnosed following an initial, usually neonatal presentation with cholestasis. Typical of these are alpha-1-antitrypsin deficiency, familial cholestasis, Alagille syndrome, and CF. Metabolic liver diseases in which the defect is expressed in the liver, leading to significant injury of other organs, should also be considered for liver transplantation, as the disease is cured by liver replacement. Each case has to be considered on its merits, in relation to mortality risk, such as in ornithine transcarbamylase deficiency and some urea cycle disorders, risk to the end-organ, such as the brain (in the case of hyperammonemic syndromes and Crigler–Najjar syndrome) and the kidney (as in hyperoxaluria), and the poor quality of life associated with these disorders.

PALF presents most commonly with new-onset jaundice, variable encephalopathy, a coagulopathy, hypoglycemia, and markedly elevated transaminases. By definition, there is no known chronic liver disease, a coagulopathy uncorrected by vitamin K, where the prothrombin time (PT) >15 seconds, and the INR >1.5, and if no encephalopathy, a PT >20 seconds, and INR >2.0 (Figure 29–2).The peak age of onset is in infancy (25% of cases), where jaundice is late feature, early hypoglycemia is common, and most cases are of indeterminate cause.[5] There is another peak of incidence in adolescents, where the etiology is more likely drug toxicity or viral. A good clinical history concerning onset, history of exposures to drugs, viruses, toxins, extrahepatic symptoms, rate of progress of symptoms and signs, and family history may point to an etiology, but at least 50% of cases are idiopathic. Signs of acute hepatic encephalopathy can be staged for monitoring and prognostic purposes, and vary according to age, as listed in Table 29–4. Some metabolic diseases causing ALF can have apparent encephalopathy due to non-hepatic causes, such as hypoglycemia and lactic acidosis. Early referral of suspected cases of PALF to a transplant program is vital, where intensive aggressive supportive therapy can be instituted, urgent attempts at determining the etiology can be instituted, and patients can be listed for a donor search if transplantation is considered an option (Figure 29–3).

Primary liver tumors in children present most commonly as an incidental finding of a painless enlarging

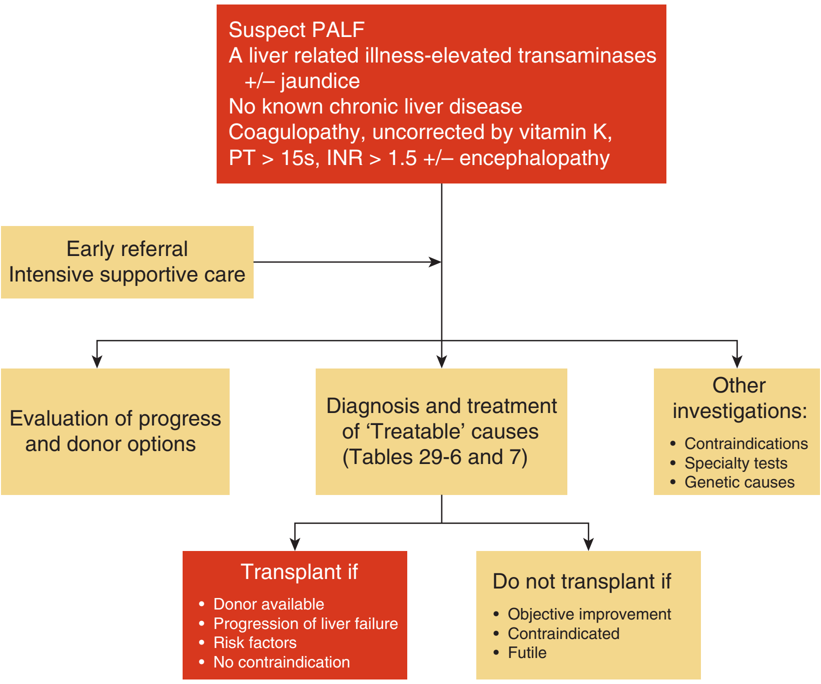
Suspect PALF
A liver related illness-elevated transaminases +/– jaundice
No known chronic liver disease
Coagulopathy, uncorrected by vitamin K,
PT > 15s, INR > 1.5 +/– encephalopathy
Early referral
Intensive supportive care
Evaluation of progress and donor options
Diagnosis and treatment of 'Treatable' causes (Tables 29-6 and 7)
Other investigations:
• Contraindications
• Specialty tests
• Genetic causes
Transplant if
• Donor available
• Progression of liver failure
• Risk factors
• No contraindication
Do not transplant if
• Objective improvement
• Contraindicated
• Futile

FIGURE 29–3 ■ Management algorithm of suspected pediatric acute liver failure (PALF).

abdominal mass, or sometimes found on abdominal exam after presentation with abdominal discomfort, pallor, or weight loss, confirmed on imaging studies (Figure 29–4). Total surgical excision and adjunctive chemotherapy are cornerstones of treatment of primary hepatic malignancies in children, and the only option for total surgical excision for unresectable tumors is liver transplantation, which has good long-term outcomes. It is generally recognized that survival after rescue transplantation after incomplete resection is poor, and thus timely assessment for transplantation in the setting of questionably resectable tumors is indicated.[7] Consultation with a transplantation program at the time of diagnosis and assessment before any chemotherapy should avoid inappropriate attempts at resection and allow appropriate planning of transplantation in relation to chemotherapy.

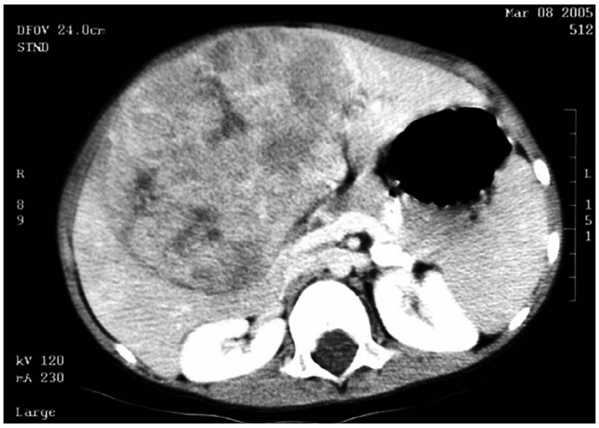

FIGURE 29–4 ■ Computerized tomography of the liver from a child presenting with vague abdominal pains, and a palpable mass on abdominal examination. A central, bilobar tumor without a plane of resection where liver transplant is the only method for complete resection.

TREATMENT

Liver Transplantation Evaluation and Preparation

The primary goals of the evaluation process (Table 29–5) are to (1) identify the risks versus benefits of transplantation; (2) identify the need for and timing of transplantation; (3) identify technical feasibility and appropriate donor options; (4) establish a pre-transplant management plan; (5) have fully informative, frank discussion of the above with the parents, and patient if possible, to help prepare them to accept and deal with all the issues and possible outcomes of the procedure. The steps taken in this evaluation are detailed in Table 29–5.

Pre-transplant Management

The primary goal of pre-transplant treatment is to keep the patient as well as possible for as long as possible, by a combination of proactive monitoring, active aggressive treatment of complications of liver disease, and multi-

Table 29–5.

Pre-transplant Evaluation

1. Establish the need for and urgency for transplantation
2. Assess technical feasiblity. Abdominal ultrasound with Doppler, size of portal vein on US, vascular studies if necessary
3. Consider severity of liver disease (PELD score or exception), based on liver synthetic function, other risk factors, risks, and possible contraindications
4. Assessment of donor options—blood group, size, suitability for reduced-size or split-liver donation
5. Identification of complications of liver disease and extrahepatic conditions
   - Nutritional status—global (weight, height, fat folds, mid-am muscle), vitamin, protein, and mineral levels
   - Portal hypertension—ascites, varices on endoscopy, hypersplenism
   - Cardiac assessment, including echocardiogram
   - Repiratory assessment: If cyanosed, perform O_2 saturation, bubble test, ventilation/perfusion, and pulmonary function testing
   - Renal function tests
   - Neurodevelopmental assessment
   - Dental assessment
   - Immunization status, and serology for CMV, EBV, varicella, measles, hepatitis A, B, and C serology
6. Evaluate social systems, issues, and logistic issues
7. Prepare the patient and parents by full, frank discussion
8. Develop a pre-transplant active management plan including
   - Immunization update
   - Nutritional support
   - Ongoing monitoring
   - Psychosocial support
   - Aggressive management of other complications of liver disease—ascites, coagulopathy, variceal bleeding, encephalopathy, and infections

disciplinary psychosocial support. Good communication systems should be in place between primary physicians and transplant centers to facilitate involvement, set expectations, manage medical and non-medical issues, and provide guidance for both families and all health care professionals toward the common goal of achieving a good outcome for the patient. Because of their long-term relationship with patients and families, primary care physicians/pediatricians are in an advantageous position to detect the early signs of complications, and help families cope with this stressful time.

End-stage chronic liver diseases

The pre-transplant management plan while on the waiting list is developed by the transplant team, in conjunction with the primary care physician, and the family (Table 29–5, item 8). Key features include immunization update, nutritional support, regular monitoring of progress, including active management/notification of intercurrent illness, psychosocial support, and active treatment of complications of liver disease.

Immunization update It is important to ensure that routine immunizations are up to date, and that protection for pneumococcus, *Haemophilus*, and hepatitis A and B be prescribed if possible, and any vaccination requiring live vaccines is administered prior to transplantation.

Table 29–6.

Nutritional Support for End-stage Liver Disease

Vitamin	Received Dose	Preparation
A	5–25,000 IU/day	"Water soluble[*]" ADEKs[†] Aquasol IV[‡]
D	600–2000 IU 0.02 μg/kg	ADEKs Drisdol[§] 1–250 HD IV[**]
E	50–100 IU	"Tocopherol polyethylene glycol succinate"
	15–25 IU/kg	Liqui E[††] Aqua E[‡‡] ADEKs
K	2.5–10 mg^2/week	Mephyton[§§] Aqua Mephyton injection

Provide adequate absorbed calories—high-energy, semi-elemental supplements, for example, Pregestimil for infants and Peptamen Junior for children. Supplement protein with branched chain amino acids, for example, Tarvil 5 g/20 mL. Avoid fasting and provide calories by nocturnal N/G or G-tube feeding if necessary. Additional fat-soluble vitamins A, D, E, and K.

[*] *Also provide minerals: calcium, zinc ,and phosphate.*

[†] *Axcam.*

[‡] *Mayne.*

[§] *Sanofi Winthrop.*

[**] *Abbott.*

[††] *Twinlab.*

[‡‡] *Yasoo.*

[§§] *Merck.*

Nutritional support The liver has a central role in regulating fuel and metabolism, nutrient homeostasis, and absorption of a number of nutrients (Table 29–6). These factors result in a catabolic state, particularly during fasting, a deficiency of proteins and calories, which, when combined with anorexia and a poor intake, make

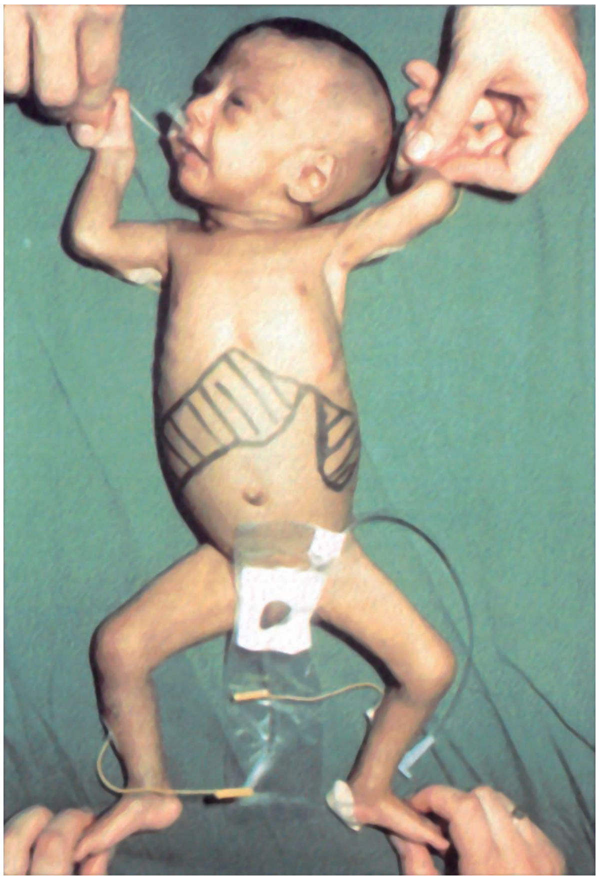

FIGURE 29–5 ■ Malnutrition is a significant potentially modifiable risk factor adversely affecting outcome in children with chronic liver disease, both before and after transplantation, making nutritional support a major focus of pre-transplant management.

malnutrition common in chronic liver disease, particularly if the onset is in infants (Figure 29–5). Malnutrition itself may induce further derangements of liver function because the liver requires energy for a number of synthetic, storage, and detoxification functions. Thus, poor nutritional status is a significant but potentially modifiable risk factor adversely affecting outcome both before and after transplantation, making nutritional support a major focus of pre-transplant management. Efforts to optimize nutritional support by providing adequate protein energy, avoiding fasting, and using specialized amino acid and vitamin formulations including enteral nutritional supplementation can improve nutritional status.

Regular monitoring While on the waiting list, regular medical monitoring is essential. The progression of the liver disease is evaluated by recalculation of the PELD score at intervals, and assessment for development of complications of liver disease, which should be aggressively treated (see below). Any change in mortality risk should prompt re-evaluation of donor options, particularly if cadaver donors via the organ sharing system are likely limited because of size or blood group constraints. Similarly, any intercurrent illness needs aggressive management, and notification to the transplant center.

Psychosocial support Families and patients find the waiting time very stressful. Mortality on the waiting list, although improved as a result of earlier referral and access to more donor options, is still a possibility. Ongoing counseling and preparation of a fully informed child and family through a multidisciplinary approach, including primary care physicians and family members as part of the team, is essential. The pre-transplant and post-transplant morbidity and mortality and the need for long-term immunosuppression require full, frank discussion, and acceptance of these risks as well as the potential benefits is arguably the most important part of the preparation of a family for liver transplantation.

Treatment of complications of chronic liver disease *Ascites* is a common complication of cirrhosis, and it is a sign of advanced liver disease (Table 29–7). Extravascular fluid accumulation in chronic liver disease represents a breakdown of intravascular volume homeostasis, which is controlled by capillary hydrostatic pressure and plasma colloid osmotic pressure. This process may develop insidiously or be precipitated by events such as gastrointestinal bleeding, infection, or the development of hepatoma. It is manifested by abdominal distension, pitting edema, sometimes pleural effusion, and/or the development of hernias. Treatment includes nutritional support, the judicious use of aldosterone antagonist and thiazide diuretics, and maintenance of plasma oncotic pressure by albumin infusion, but in some cases this becomes refractory. Tense ascites may require large-volume paracentesis and albumin infusion.

Coagulopathy in chronic liver disease is due to a combination of vitamin K malabsorption and deficiency, reduced synthesis of coagulation factors, and thrombocytopenia secondary to hypersplenism. These disturbances are particularly important in prognostic assessment, and in the genesis and management of gastrointestinal bleeding, and may lead to serious complications such as intracerebral bleeding and intravascular consumption coagulopathy. Management is directed at prevention/correction of vitamin K deficiency with oral or parenteral vitamin K supplements. If refractory, or there is active bleeding, or high risk of bleeding or for procedures, fresh frozen plasma infusions, platelet infusions, or the use of desmopressin may achieve temporary hemostasis.

Variceal bleeding, one of the major causes of morbidity and mortality, is a manifestation of portal hypertension, caused by a combination of increased portal blood flow and increased portal resistance. Signs and symptoms of portal hypertension are primarily the result of decompression of this elevated portal blood pressure through portosystemic collaterals, manifest as splenom-

Table 29–7.

Treatment of Complications of Chronic End-stage Liver Diseases

Ascites
Nutritional support
Avoid sodium intakes >2 mmol/kg
Spironolactone ± chlorothiazide, for example, Aldactazide: <3 years 12.5 mg qid, >3 years, up to 50 mg qid
Albumin infusions (if serum albumin >25 g/L) in a dose of 2 g/kg + frusemide 2 mg/kg
If refractory and symptomatic—paracentesis + albumin infusion

Coagulopathy
Vitamin K supplements (see Table 29–5)
Fresh frozen plasma 10 mL/kg—active bleeding, invasive procedures, PT >40 seconds, unresponsive to vitamin K
Platelet infusion—for active bleeding and count <20,000
Desmopressin—for active bleeding with global coagulation protein deficiencies (ii, vii, ix, x)

Variceal bleeding
Secure IV access, and hemostasis with vitamin K and fresh frozen plasma
Treat hypovolemia with blood transfusion and stabilize patient
Administer short-acting splanchnic vasoactive agent, for example, octreotide 25 mg/hour IV
Refer to center experienced in pediatric endoscopy, transcutaneous shunts, and liver transplantation
Prevent recurrence with endoscopic ablation, beta-blockers
Liver transplantation

Encephalopathy
Avoid precipitating factors
Avoid prolonged fasting, ensure nutritional support
Lactulose 0.4 mL/kg/day and PO vancomycin divided into three doses

Bacterial infections
High index of suspicion in biliary atresia (cholangitis) or ascites (primary peritonitis)
Minimize risk by nutritional support, active Rx of ascites, immunization for pneumococcus, hemophilus
Prophylactic antibiotics for invasive procedures, prevention of recurrence
Bacteriological studies and early institution of an extended-spectrum beta-lactam antibiotic

egaly and hypersplenism, the development of ascites, and the occurrence of esophageal, gastric, and rectal varices. Splenomegaly and hypersplenism rarely require specific intervention, and ascites is considered above. Bleeding from esophageal varices may be life-threatening and may precipitate liver failure, and requires prompt diagnosis and treatment (Figure 29–6). Salient points include: a secure intravenous infusion line; urgent blood transfusion; achieving hemostasis via parenteral vitamin K and plasma infusion; consideration for octreotide

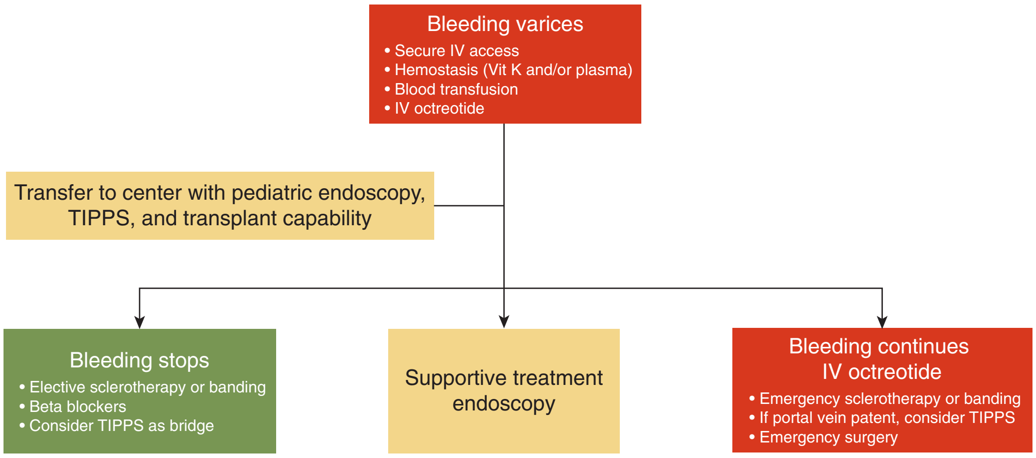
Bleeding varices
• Secure IV access
• Hemostasis (Vit K and/or plasma)
• Blood transfusion
• IV octreotide
Transfer to center with pediatric endoscopy, TIPPS, and transplant capability
Bleeding stops
• Elective sclerotherapy or banding
• Beta blockers
• Consider TIPPS as bridge
Supportive treatment endoscopy
Bleeding continues IV octreotide
• Emergency sclerotherapy or banding
• If portal vein patent, consider TIPPS
• Emergency surgery

FIGURE 29–6 ■ Management algorithm for upper gastrointestinal bleeding in children with chronic liver disease.

infusion; and referral (when stable) to a tertiary center with experience in endoscopic sclerotherapy or banding, transcutaneous intrahepatic portosystemic shunts (TIPSS), and liver transplantation. Prevention of recurrence with vasoactive pharmacotherapy (e.g., beta-blockers), endoscopic ablation, or TIPSS may be indicated as a bridge to transplantation, but surgical shunts are best avoided in prospective transplant patients.

Encephalopathy in children with chronic liver disease is difficult to recognize, particularly in infants. Pathogenesis is related to four major processes: portosystemic shunting, hepatocellular dysfunction, interaction of nitrogen metabolites from the intestine with the central nervous system, and altered neurotransmitter function. Early symptoms are subtle and include neurodevelopmental delay, school problems, lethargy, or sleep reversal (somnolent by day and insomnia by night). Intellectual impairment and personality change may occur in older children, while clouding of consciousness, asterixis, ataxia, stupor, and coma are late signs, these tending to develop in conjunction with precipitating events, such as gastrointestinal bleeding or the use of sedatives. It is also common following shunts for portal hypertension. Treatment is directed at removing precipitating factors, avoidance of fasting, and reducing intestinal protein load with lactulose, and broad-spectrum antibiotics (Table 29–7). Protein restriction is not usually necessary, and not recommended in children due to the risk of further nutritional compromise.

Bacterial infections may precipitate other complications, such as encephalopathy, ascites, and hepatorenal syndrome, and are predisposed to liver disease by immune dysfunction, neutropenia, and alterations in mucosal barriers. Portal hypertension makes patients susceptible to bacteremia, perhaps by inducing bacterial translocation of the gut. Spontaneous bacterial peritonitis is a serious complication of ascites and should be considered in all children with ascites who show signs of sepsis. In BA, recurrent cholangitis is a risk factor for death on the waiting list. Urinary and respiratory tract infections are also frequent, and bacteremia commonly results from invasive investigations. Other risk factors for infection are low serum albumin, gastrointestinal bleeding, ascites, intensive care unit admission for any reason, and endoscopy. Certain agents are more virulent and more common in patients with liver disease, including *Klebsiella*, *E. coli*, *Campylobacter*, *Yersinia*, *Plesiomonas*, *Enterococcus*, *Aeromonas*, and *Listeria* species. Preventative measures such as pneumococcal and *Haemophilus* vaccination, prophylactic antibiotics for invasive procedures, nutritional support, and management of ascites may reduce risk. When infection is suspected, immediate bacteriological studies and early institution of antimicrobial therapy with a broad-spectrum antibiotic (e.g., an extended-spectrum beta-lactam antibiotic such as tazobactam + piperacillin (Zosyn)) are recommended, while awaiting culture and sensitivities.

Table 29–8.

Medically "Treatable" Causes of PALF

Drugs and toxins

- Acetominophen—*N*-acetyl cysteine (NAC) by continuous infusion
- *Amanita phalloides*—steroids, silibinin, penicillin
- Others—cease/avoid the drug

Immune diseases

- Autoimmune hepatitis—steroids/azathiaprine
- Hemophagocytic (macrophage activation) syndrome—high-dose of steroids, etopaside, cydosporin

Metabolic liver diseases

- Tyrosinemia I—nitisinone (NTBC)
- Wilson's disease—chelation with penicillamine, zinc
- Galactosemia—lactose-free diet
- Neonatal hemochromatosis—antioxidant "cocktail" -IV NAC, selenium 3 mcg/kg/day
- Tocopherol PEG succinate 25 IU/kg/day, vitamin C 25 mg/kg/day

Viral infections

- Herpes viruses—acyclovir
- Enteroviruses—pleconaril
- Other viruses—consider IVIG

Pediatric acute liver failure

Whenever PALF is suspected, as indicated above and in Figure 29–3, early referral to a transplant center is advisable. Key features of management involve simultaneously supporting the patient, evaluating the cause, particularly medically "treatable" causes (Table 29–8), monitoring the progress of the liver failure, and assessing possible donor options in case liver transplant is available.[5] However, 50% of cases recover without transplantation, that is, 50% will die without transplantation, there are some contraindications, and some situations where a transplant becomes futile.

Supportive measures Most cases require intensive care, with aggressive management of coagulopathy and encephalopathy, often requiring ventilatory and hemodynamic support. Hepatorenal syndrome and infection are not uncommon complications that require further aggressive management. Medical treatment for "treatable" causes should be instituted without delay (Table 29–8). *Investigations* are listed in Table 29–9, and are divided into those required for monitoring and supportive treatment, those required to rule out medically "treatable" causes, and those to evaluate other known

Table 29–9.

Investigating Pediatric Acute Liver Failure

Routine patient monitoring

- Hematology—FBC, ESR, reticulocyte count
- Coagulation—PR/INR, APTT, fibrinogen, factor V
- Glucose homeostasis
- Blood gases
- Blood/urine cultures
- Liver bilirubin tests —direct/indirect, ALP, GGT, AST, ALT, total protein, albumin, globulins
- Biochemistry—sodium, potassium, BUN, creatinine, calcium, phosphate, magnesium, chloride, amylase, uric acid, ammonia
- ECG, echocardiogram
- Imaging CXR, abdominal ultrasound and Doppler, head CT if cornatose

"Treatable" causes of PALF

- Infant—neonatal iron storage, tyrosinemia, fructosemia, galactosemia
- Specific investigations—ferritin
- Urine-reducing substances and galactose-1-phosphate uridyltransferase plasma and urine organic acids, amino acids, urine succinylacetone
- Child/adolescent—acetaminophen toxicity, autoimmune hepatitis, Wilson's disease
- Specific investigations—acetaminophen level
- IgG, protein electrophoresis, 24-hour urine copper, split lamp eye exam, liver biopsy

Other diagnostic tests

- Virology HBV, CMV, EBV, HAV, HCV, HSV, HIV, varicella, measles, parvovirus, HHV-6 PCR
- Serology toxoplasmosis, leptospirosis
- Special tests
- Fasting pyruvate/lactate
- Acylcarnitine profile
- Alpha-fetoprotein
- Very-long-chain fatty acids
- Plasma and urine organic acids, amino acids
- Plasma and urine toxicology screen
- Bone marrow
- Skin biopsy
- WBC enzymes
- Muscle biopsy
- Abdominal ultrasound and Doppler
- Liver biopsy

causes, including those where transplant might be contraindicated.

Indications for transplantation Unless there is a contraindication to transplant, most patients are listed for a donor search, and the decision as to whether to proceed is made when a donor becomes available. The decision to go ahead with a transplant at that time is based on rate of progression of liver failure or lack of signs of improvement, and the presence of defined poor prognostic indicators, including age <1 year, progressive encephalopathy, vitamin K-unresponsive PT >40 seconds and INR >4, hypoglycemia with ongoing high dextrose requirement, serum bilirubin >300 μmol/L (17.5 mg/dL), a rapid reduction in liver size clinically (plus precipitous fall in AST), and/or no regenerative features and extensive hepatic necrosis (<20% viable hepatocytes/HPF) on liver biopsy. For acetaminophen liver injury, where specific treatment with *N*-acetyl cysteine should be instituted, consider transplant if pH <7.3, creatinine >0.3 mmol/L, and/or INR >6.5 with no improvement on treatment. While waiting for a donor organ, if there are signs of stabilization or evidence of recovering function (improved coagulation parameters and encephalopathy), transplantation may be deferred. Similarly, if circumstances arise in which a transplant becomes futile, then transplantation is not indicated. Examples include uncontrolled systemic sepsis, irreversible neurological injury, or a diagnosis of underlying non-hepatic disease, such as malignancy or a mitochondrial disorder.

Post-transplant Management

The goals of post-transplant management are to manage and treat postoperative complications, and develop a balanced long-term immunotherapy regimen that minimizes infection and side effects but controls rejection (Figure 29–7). There must be provision for long-term follow-up, with proactive treatment of common problems. As with pre-transplant management, good communication systems should be in place between primary physicians and transplant centers. Because of their accessibility and long-term relationship with patients, primary care physicians are in the best position

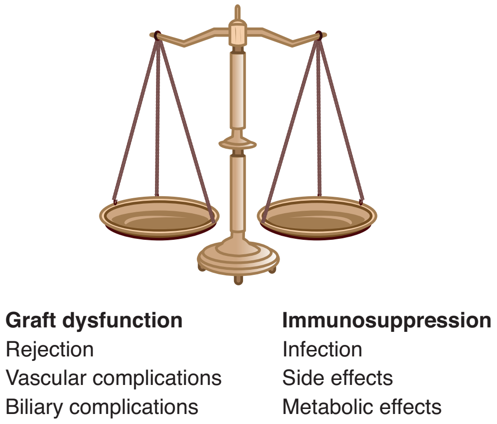

FIGURE 29–7 ■ Post-transplant management. The ideal balance in immunotherapy, graft function, and patient well-being.

to detect the early signs of complications, recognize or suspect poor compliance with immunosuppressive therapy, manage common problems, and provide ongoing support to families.

Although most children who have had liver transplants can expect cure of their liver disease and improved quality of life (see the section "Outcomes"), they require indefinite follow-up and often require medical attention for complications or co-morbid conditions related to their immunosuppressive drug therapy. While modern immunosuppressant regimes have reduced rates of graft loss due to rejection, they impart major risks for infection, growth failure, metabolic complications, and malignancy.[4,8,9] Indeed, there is significantly more post-transplant morbidity and mortality from infection than from rejection, particularly in infants. This has led to a trend toward minimization of immunosuppression, which is supported by evidence that some rejection facilitates graft tolerance and thus is not necessarily always harmful in liver transplantation (as distinct from other solid organ transplants).

Complications after liver transplantation

Serious post-transplant complications are divided into those that occur in the first 3–12 months ("early"), and these are relatively common, and those occurring after 12 months ("late"), which are generally uncommon (Table 29–10). In addition, there are many common medical issues, and some specific long-term issues that require medical attention in relation to the long-term use of immunosuppressive medications (Table 29–11). Most "early" complications relate to surgical issues, and/or immunosuppression, most notably infection, vascular complications of the graft, and biliary leaks. Infection (detailed below) is the most common cause of post-transplant mortality.[9] Rejection (see below) does occur but usually responds to treatment with steroid pulse dosing, and appears not to contribute to either graft or patient mortality. "Late" complications include biliary strictures, which are uncommon and generally respond to percutaneous biliary dilatation and stent procedures. Most late complications are primarily related to the effects of long-term immunosuppression, notably infections such as Epstein–Barr virus and associated post-transplant lymphoproliferative disease (PTLD), warts, skin cancers, and side effects of immunosuppression such as renal dysfunction, hypertension, and immune dysregulation. Late or chronic rejection is most often a manifestation of compliance, and late graft losses are most commonly related to this.

Outline of immunosuppression regimens

There is some variability among transplant centers in the details of immunosuppressive therapy. The goals are to avoid rejection and graft injury, to encourage some

Table 29–10.

Post-transplant Complications

'Early': first 12 months

- First month
  - Primary graft non-function
  - Vascular complication
  - Infections/bacterial sepsis
  - Wound and drain issues
  - Biliary leaks
  - Intra-abdominal fluid collections
  - Rejection
- 1–3 months
  - Infections (CMV, EBV)
  - Biliary strictures
  - Hepatic vein stenosis
  - Rejection
- 3–12 months
  - PTLD
  - CMV infections
  - Biliary strictures
  - Rejection
  - Hypertension
  - Poor growth

"Late" >12 months

- PTLD
- Unusual infections
- Renal dysfunction
- Hypertension
- Non-compliance with medications
- Growth failure
- Late biliary strictures

Table 29–11.

Post-transplant Immunization Schedule for Liver Transplant Recipients

Starting 6 months post-transplant	
Hepatitis B	6, 8, 10 months if not previously given
DTP	Resume standard schedule
H. influenzae type b	Resume standard schedule
Polio	Resume standard schedule; patient and siblings must receive inactivated polio vaccine*
Measles, mumps, rubella	At 6 months if not previously given, confirmed by vaccine response with titers
Varicella	At 7 months if not previously given, confirmed by vaccine response with titers†
Pneumavax	Required for patients with splenectomy or asplenia‡
Hepatitis A	At 12 months
Influenza	Yearly

**NA live viruses.*
†Patients may experience low-grade fever and vesicles at injection site.
‡Penicillin prophylaxis is also recommended for these patients.

early allorecognition (not necessarily to eliminate rejection altogether), and to minimize immunosuppressive side effects.[4,8,9] Most commonly, the immunotherapy plan is based on initial high-dose steroids, progression to oral steroids, introduction of an oral calcineurin inhibitor (CNI), usually tacrolimus (TAC), and oral mycophenylate mofetil (MMF), with individualized progressive tapering and cessation of steroids over 3–12 months, followed by cessation of MMF. Some centers include induction therapy with monoclonal antibodies to reduce the need for steroids. Most patients achieve low-level TAC monotherapy by 12–24 months post-transplant. The use of cyclosporine, an earlier CNI, is declining because of a higher side-effect profile. TAC, 0.15–0.3 mg/kg/day, is administered orally, with titration of TAC dose to achieve trough levels between 8 and 10 ng/mL on routine monitoring over the first 12 months, beyond which levels of around 5 ng/mL are considered acceptable. If used, MMF is given orally at 150–600 mg/m^2/dose and is discontinued after a rejection-free interval of 3–6 months post-transplant. Patients aged <1–2 years, patients with primary liver tumors, or patients who are leukopenic, with white blood count <3000, are not given MMF. Monitoring of kidney function is important in patients on CNIs, assessed by occurrence of systemic hypertension, and serial measurement of serum creatinine. In addition, creatinine clearance studies are done after 1 and 3 years.

Infection prophylaxis and surveillance

Prophylactic antibiotics are given intravenously for 48 hours post-transplant, and then usually discontinued. Any invasive procedure thereafter is usually managed with antibiotic cover, including dental procedures. A prophylactic antifungal agent (such as fluconazole) is administered orally for 2–3 months. Prophylactic antiviral medications are used in all patients. Acyclovir is prescribed for 3 months if both donor and recipient were CMV and EBV negative, and ganciclovir for 6 months if either donor or recipient was positive for either CMV or EBV. CMV and EBV naive patients have surveillance serum CMV and EBV viral load by polymerase chain reaction (PCR), usually on a monthly basis while heavily immunosuppressed, or as indicated if there is presentation with an illness. A post-transplant *immunization schedule* is summarized in Table 29–11. Despite these precautions, serious bacterial infections occur in about one-third of patients, mostly in the first 3 months post-transplantation, and serious viral infections caused by CMV or EBV occur in about 10% of patients.[8,9] Risks for bacterial/fungal infections included young recipient age, Hispanic race, use of donor organ variants, higher bilirubin, prolonged anhepatic time, and use of cyclosporine instead of TAC.[9] Serious viral infection risks include young age (PTLD is 10-fold higher in infants), donor organ variants, and experiencing rejection episodes causing immunosuppression to be increased. Any illness characterized by fever, respiratory, abdominal, urinary, or gastrointestinal symptoms requires careful evaluation, and, in selected cases, viral, bacterial, and other diagnostic workup. Empiric preemptive therapy should be used as indicated.

The cornerstone of treatment for serious infections is the temporary reduction or cessation of immunosuppression, along with appropriate antiviral or antimicrobial drug therapy. PTLD caused by Epstein–Barr virus is a potentially life-threatening consequence of CNI therapy, resulting in inability of the immune system to control the proliferation of EBV-infected B cells. Presenting features are variable, and include mononucleosis-like symptoms (fatigue, fevers, and lymphadenopathy), or localized or disseminated lymphoproliferation with tumors involving the lymph nodes, liver, lung, kidney, bone marrow, central nervous system, or small intestine. Because increases in EBV viral load in peripheral blood typically precede the development of PTLD, measurement of viral load by quantitative PCR is useful in monitoring. Tissue biopsy of associated tumors shows plasma cell hyperplasia, B-cell hyperplasia, B-cell lymphoma, or immunoblastic lymphoma. Immunostaining can be used to reveal the clonality of the proliferating B cells in these tumors or in circulating leukemic cells. These may be monoclonal, oligoclonal, or polyclonal; patients with polyclonal lesions have the best prognosis. The diagnosis is confirmed by demonstrating EBV proteins in biopsy tissue. Treatment involves cessation or reduction of immunosuppression, surgical removal of local lymphoproliferative lesions, especially in the gastrointestinal tract, ganciclovir, monoclonal-antibody therapy with rituximab, a monoclonal antibody directed against the CD20 B-cell antigen, and in some cases cytotoxic chemotherapy. The latter has been effective for patients with lymphoma or who have had no response to a reduction in the dose of immunosuppressive drugs or to other therapies. Complete cessation of CNIs is used in high-risk patients with low rejection risk (young age and use of cyclosporine or antilymphocyte products).

Monitoring, diagnosis, and treatment of rejection

Routine monitoring of liver biochemistry and CNI trough levels is undertaken frequently during the early post-transplant period, reducing to monthly, unless otherwise indicated. Rises in transaminases without any evidence for biliary or vascular etiology or intercurrent illness are presumptive for acute cellular rejection (ACR) without biopsy. Doubtful cases require diagnostic liver biopsy. Rejection episodes are treated with a 3-day pulse of prednisone (2–5 mg/kg/day) and an increase in TAC to temporarily achieve trough levels of 10–12 ng/mL. If patients do not respond to a 3-day steroid pulse, then other options include higher dose intravenous steroid pulses, and/or addition of other immunosuppressive drugs. As noted above, rejection rarely is a factor in patients of graft losses.[4,8,9] Risks are lowest in infants, higher in adolescents, and highest in those of any age receiving blood type-mismatched organs.[9] Biopsy-proven chronic rejection is uncommon, and is treated with continuation of TAC to achieve levels of 10–12 ng/mL, and the addition of azothioprine at 2 mg/kg/day. In adolescents, this chronic rejection is most commonly related to poor compliance.

Common problems

Patients on long-term immunosuppression are bound to encounter issues related to *common illnesses* such as vomiting, diarrhea, and fevers (Table 29–12). These illnesses should be treated on their merits, but generally always require medical consultation, in case of serious or progressive illness. Missed immunosuppressant medications should not be double dosed, but simply resumed at normal doses as soon as possible. Gastroenteritis illnesses often spuriously result in elevated TAC levels and mild elevations of liver transaminases. *Infection contacts*, particularly with serious viral infections such as *varicella*, require consideration of prophylactic therapy. *Regular dental care* is mandatory, due to the frequency of pre-existing poor dentine, high caries rate and delayed tooth development in patients with liver diseases, and the need for ongoing dental hygiene in immunosuppressed patients. Major dental work requires prophylaxis with antibiotics because of high occurrence of bacteremia during these procedures.[10] *Compliance with medications* is a common issue in adolescents particularly, and poor compliance can have serious consequences. This is suspected when monthly surveillance TAC levels show a large variability, and/or there are unexplained increases in liver transaminases. Systems such as mobile phone reminder, text messages, daily diaries, and closer monitoring have been shown to improve compliance.[11] *Unexplained elevations of transaminases* should be evaluated. Although most are temporary due to intercurrent illness or lapses in compliance, persistent changes could indicate late graft dysfunction and require investigation with imaging and/or liver biopsy. Follow-up of growth and development with yearly monitoring is the norm for all pediatric transplant recipients. Deviations require more detailed evaluation and treatment. *Skin conditions* such as eczema and warts are more common in immunosuppressed patients. These often require specialist referral and management. Skin cancers should be minimized with active lifelong solar prophylaxis. Finally, issues of *fertility and pregnancy* are increasingly being raised in long-term survivors of pediatric liver transplantation. Many successful pregnancies have been recorded, and the current evidence suggests that pregnancy is safe after transplant.[12,13] Pregnancy does require close management by a team of experienced physicians. Significant experience has indicated that the use of CNIs, azathioprine, and prednisolone is safe during pregnancy, but few data are available for newer immunosuppressants such as MMF, and thus these agents are not recommended.[13,14]

Table 29–12.

Common Issues in Post-transplant Follow-up

Managing Common Problems	Managing Specific Problems
Vomiting	Compliance
Diarrhea	Liver dysfunction
Fever	Growth
Missed medications	Development
Infection contact	Skin problems—warts, eczema, solar cancers
Dental care	Pregnancy and fertility

OUTCOMES

Patient and Graft Outcomes

Current 1-year patient and graft survival rates across pediatric centers of expertise are 90–95% and 80–85%, respectively, and at 3 years approximately 85% and 80%, with only minimal decline after that.[4,8] These overall good outcomes have been achieved by early referral with excellent pre-transplant care (particularly of hepatic complications and nutritional support), the improved donor options mentioned above, and advances in post-transplant management, particularly more targeted and age-specific immunosuppression. Unfortunately, there is still a small but significant risk of dying while on the waiting list. Waiting list mortality risk factors include the infant age group, a high PELD score of ≥20, poor nutrition, and acute liver failure.[4] Early post-transplantation mortality risk factors include infant recipients, poor nutritional status, need for re-transplantation, usually secondary to surgical complications, and acute liver failure.[4] Overall, infection is the single most important cause of death, contributed to by immunosuppression and surgical complications.[9] Early episodes of rejection (<6 months after transplantation) do not contribute to mortality or graft failure. Graft failure risks include poor nutrition, the use of cadaveric reduced-size donor segments, the use of cyclosporine versus TAC, and recurrent/chronic rejection.[4,9]

Functional and Long-term Outcomes

With careful follow-up management and close attention to detail, most pediatric liver transplant recipients can expect an excellent long-term outcome. There is remarkable recovery from the effects of their liver or metabolic disease, an expectation of long-term survival with good graft function, catch-up growth (albeit sometimes incomplete), and a good quality of life.[8,15] In general, in the first 5 years post-transplant, parents report higher emotional stress and disruption of family activities compared to a normal population, although the level of family function appears normal. At 10 years post-transplant, >95% of survivors have normal graft function, and self-report good to excellent quality of life and normal school achievements.[16,17] Non-adherence to the medical regimen is perhaps the most important predictor of late graft dysfunction, and health-related quality of life may independently correlate with non-adherence. As improvements are being realized in long-term immunosuppression regimens, notably minimizing immunosuppression, a diminishing number of patients suffer long-term complications of immunosuppression. These include altered diabetes, decreased renal function, hypertension, cancer, and osteopenia.

Information on Outcomes

In the United States, all transplants and transplant outcomes are monitored by the Organ Procurement and Transplant Network (OPTN), whose primary purposes are to operate and monitor equitable allocation of organs donated for transplantation, maintain a waiting list of potential recipients, match recipients with donor organs according to established criteria, and facilitate the efficient, effective placement of organs for transplantation. Outcome data are available in the public domain, and practitioners and families can view national, regional, and individual center risk-adjusted waiting times, and outcomes by accessing the OPTN website.

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